AD_____

Award Number: DAMD17-98-1-8600

TITLE: A Micro-Simulation Model of the Benefits and Costs of Prostate Cancer Screening and Treatment

PRINCIPAL INVESTIGATOR: David O. Meltzer, M.D., Ph.D.

CONTRACTING ORGANIZATION: University of Chicago
Chicago, Illinois 60637

REPORT DATE: July 2000

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	July 2000	Annual (1 Jul 99 - 30 Jun 00)

4. TITLE AND SUBTITLE
A Micro-Simulation Model of the Benefits and Costs of Prostate Cancer Screening and Treatment

5. FUNDING NUMBERS
DAMD17-98-1-8600

6. AUTHOR(S)
David O. Meltzer, M.D., Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Chicago
Chicago, Illinois 60637
E-MAIL: dmeltzer@medicine.bsd.uchicago.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

Our project is completing work on an innovative model to determine the cost-effectiveness of alternative prostate cancer screening strategies. Indeed, prostate cancer screening remains controversial and continues to present difficult choices for patients, physicians, and policy makers. Hence, modeling the natural history, screening, and treatment of prostate cancer to better understand screening benefits and costs is potentially of great value. To date, we have reviewed every published cost-effectiveness analysis of prostate cancer screening. While these papers have many strengths, all of them have flaws that undermine their validity and relevance. We have addressed these concerns extensively in the model we have developed. We have now finished programming the model and are currently fitting the model using constrained optimization and maximum likelihood techniques. We have also performed preliminary analyses of annual screening with digital rectal exam (DRE), prostate specific antigen (PSA), or their combination. These analyses suggest that screening may be cost-effective in terms of cost per life-year saved; however, analyses in terms of cost per Quality Adjusted Life-Year (QALY) suggest that their cost-effectiveness is highly dependent on quality of life weights for health states. We will be finishing our analyses and preparing manuscripts for publication over the next few months.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Prostate Cancer	18
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

(4) Introduction

Our project is completing work on an innovative model to determine the cost-effectiveness of alternative prostate cancer screening strategies. Indeed, prostate cancer screening remains controversial and continues to present difficult choices for patients, physicians, and policy makers. Hence, modeling the natural history, screening, and treatment of prostate cancer to better understand screening benefits and costs is potentially of great value. To date, we have reviewed every published cost-effectiveness analysis of prostate cancer screening. While these papers have many strengths, all of them have flaws that undermine their validity and relevance. We have addressed these concerns extensively in the model we have developed. We have now finished programming the model and are currently fitting the model using constrained optimization and maximum likelihood techniques. We have also performed preliminary analyses of annual screening with digital rectal exam (DRE), prostate specific antigen (PSA), or their combination. These analyses suggest that screening may be cost-effective in terms of cost per life-year saved; however, analyses in terms of cost per Quality Adjusted Life-Year (QALY) suggest that their cost-effectiveness is highly dependent on quality of life weights for health states. We will be finishing our analyses and preparing manuscripts for publication over the next few months.

(5) Body

Our progress to date has closely followed the work specified in the **Statement of Work** section of our original proposal. We have been able to accomplish our specific goals with little or no delay. Major accomplishments that have occurred since our last report include our completion of an extensive literature review of the published studies concerning the costs and benefits of prostate cancer screening and treatment, and preliminary cost-effectiveness results. One major development is that we have received an extension of our proposal final deadline from the Department of Defense. We are confident that we will be able to complete our project by this revised deadline. We will outline our progress in relation to the **Statement of Work** point by point below.

Task 1. Review of model structure to reflect evolving innovation, Months 1-3.

- *a) Relevance given current knowledge of prostate biology (i.e. grade, p53, early metastases)*
- *b) Relevance given current screening and treatment technology (i.e. PSA density, % free PSA)*
- *c) Relevance for potential future technologies (i.e. PCR, Indium-111 labeled antibody to detect metastases, gene therapy)*

This task has been completed and was documented in our last annual report.

Task 2. Programming of model to reflect revised structure, Months 1-6

- *a) Revision of decision tree if needed*
- *b) Revision of natural history model if needed*
- *c) Programming of costs*
- *d) Programming of benefits and quality of life adjustments*

This task has been completed and was documented in our last annual report.

Task 3. Review of literature to estimate model parameters, Months 4-18

- a) *Identification of parameters of interest*
- *b) Collection of articles relevant for parameters of interest*
- *c) Review and analysis of articles*
- *d) Preparation of documentation of literature review*

The partial completion of many of these tasks were documented in our last annual report. At this time, we have completed our literature review and have completed a draft of our comprehensive parameter derivation documentation. We estimated model parameters by a combination of methods including 1) extensive literature review, 2) meta-analysis, 3) analysis of primary data, and 4) mathematical modeling. An example of a set of parameters that we have estimated by extensive literature review is the incidence of BPH by age.[1] An example of a set of parameters that we have estimated by meta-analysis is prevalence of occult prostate cancer in autopsy studies by age. An example of a set of parameters that we estimated by data analysis is prostate cancer treatment rates by clinical stage and age; this parameter in particular was estimated using Surveillance, Epidemiology, and End Results (SEER) data, the results of which will be published in a forthcoming article in the American Journal of Public Health. An example of a parameter for which we have used mathematical modeling is the probability that a biopsy will be positive in the presence of stage A cancer, which we modeled using a geometric model of a needle transversing a hypothetical prostate of a standard volume encountering a tumor of specified volume present in the prostate, and validated against post-mortem studies of biopsy yield in men examined for prostate cancer on autopsy.

We have also reviewed every published cost-effectiveness analysis of prostate cancer screening and treatment.[2,3,4,5,6,7,8,9,10,11,12,13,14] Our review has demonstrated to us that while many of the published papers have been carefully performed and have many strengths, all of them have major flaws that seriously undermine their validity and relevance. The first and most important of these flaws is that many of these studies fail to model prostate cancer incidence as a dynamic process that may be affected by previous screening patterns through their effects on the prevalence of latent disease in the population. As the recent rise and fall in prostate cancer evidence indicates this is clearly not the case. This flaw becomes particularly important when one attempts to model repeat screening, and as a result, every model that we are aware of except two has not even tried to model more than a one time screen.[15,16] Of these two published models of repeat screening, one is an important advance in modeling this dynamic process of disease progression, but does not incorporate any of the other innovative aspects of our model, while the other also has fundamental problems in how the process of disease progression is modeled. We discuss these issues further below. The second major flaw in existing models is that many have either failed to distinguish between cancers of differing stage and grade, or modeled progression based on clinical rather than pathologic stage. The relevance of this last distinction is that modeling progression based on clinical stage may be highly misleading when the underlying true pathologic stage associated with a given clinical stage changes as a result of changing prevalence as, for example, due to previous screening. For example, a one-time screen of a population might find many large cancers that appear to be localized based on clinical criteria, but are actually found to have spread into or beyond the prostatic capsule. A second screen would likely also find a number of additional cancers that appear to be clinically localized, but because the larger cancers were mostly found by the first screen, a larger fraction of these additional cancer are likely to actually be localized. As a result, extrapolating the benefits of treatment based on clinical stage could be misleading. We note in this regard that even the most sophisticated model of repeat screening in print to date written by Etzioni and colleagues,[16] assumes that the cure rate for clinically localized disease is either 100% in its base case analysis, and less than 100%, but still not variable by screening frequency in its sensitivity analyses. The large literature on recurrence after radical prostatectomy assures that the base case analysis cannot be correct, and the argument above suggests that even the sensitivity analysis performed is not capable of capturing how the cure rate is likely to change as screening frequency changes. This is a unique and crucial advantage of our model based on pathologic stage that we describe below. Other major advantages of our approach over Dr. Etzioni's work are that we explicitly model 1) the role of heterogeneity by tumor grade, 2) PSA and DRE sensitivity and specificity as correlated over time, 3) the effects of cohort-specific screening history on prevalence in model validation exercises, and 4) the effects of benign prostatic hypertrophy (BPH) and other prostate symptoms on the detection of prostate cancer. We should note also that Etzioni and colleagues' model only examines effectiveness, and not costs or cost-effectiveness, and that the only screening policies they consider involve screening from age 50 to age 95, which are very unlikely to be optimal given the small or negative benefits to be expected from treating men at highly advanced ages. We also note that on September 20, 2000, JAMA

published a model of repeat screening by Ross and colleagues,[15] but that this model 1) makes arbitrary assumptions about the natural history of prostate cancer ("transition probabilities were computed by setting the rate of entry into each state equal to the rate of exit from the state at 1 year older") without justification or any validation exercises, 2) does not model heterogeneity by grade (which is essential to modeling length time bias in repeat screening), and 3) misconstrues the concept of cost-effectiveness, reporting "cost-effectiveness ratios" without ever modeling costs in any way. Many of the existing models of one time screens are also flawed in other ways, including confusing the positive/negative predictive value of screening tests and the sensitivity/ specificity, failing to model effects on quality of life or costs, and a variety of more technical or data-related issues.

Our review or the literature has enabled us to develop parameters that account for several key aspects of the natural history, screening, and treatment of prostate cancer that less complex models could not. These are the ability to model:

(1) Tumor heterogeneity and progression rates by grade,

Heterogeneity by grade is known to be extremely important because it has been shown to be at least as important a predictor of progression or mortality in prostate cancer as stage.[17] This distinction is extremely important for assessing the effects of one-time versus repeated screening because repeated screening is likely to be superior to one-time screening at differentially detecting tumors most likely to progress.[18, 19] Such "length time bias" cannot be modeled by "averaging" progression rates across grades, but can be modeled when heterogeneity is explicitly accounted for.

Because our model includes heterogeneity by grade, we can use the model to show that the benefits of treatment will vary by grade of tumor, and that repeat screening may differentially identify tumors more likely to progress.

(2) Misclassification of tumor stage due to the discrepancy between clinical and pathologic stage.

Maintaining the distinction between clinical and pathologic stage is essential for explaining multiple aspects of prostate cancer screening and treatment.[20] Perhaps most striking is the fact that between one quarter and one third of men receiving radical prostatectomy for apparently localized prostate cancer eventually require further treatment, suggesting that the initial disease was not actually localized.[21] The discrepancy between clinical and pathologic stage is also essential to explain the upstaging commonly observed when a patient with apparently localized prostate cancer undergoes radical prostatectomy.[22] Since data on incidence patterns often reflect the best available staging information, maintaining the distinction between clinical and pathologic stage is important to using data on stage-specific incidence patterns for model validation. Moreover, this implies the importance of correctly describing treatment patterns according to clinical stage rather than according to best stage. Because our model accounts for the discrepancy between clinical and pathologic stage, we can use the model to show how patients treated for apparently localized disease with radical prostatectomy may nevertheless progress to require further treatment.

(3) The ability of screening and treatment to affect the prevalence of prostate cancer.

Most models of one-time screening for prostate cancer have used available data on the age-specific incidence or prevalence of prostate cancer as a basic input into the model.[8,12] However, although it is conceptually more simple to model the incidence of prostate cancer as being a given rate at each age, this is clearly not a reasonable assumption if repeated screening can affect the prevalence of undetected disease in the population. For example, the recent declines in prostate cancer incidence following the dramatic increase in prostate cancer incidence in the context of more aggressive screening in the late 1980s and early 1990s suggests that this is not just a theoretical possibility. Indeed, it is difficult to explain how increased screening can result in lower incidence unless the pool of persons with undetected cancer has been reduced.

Because our model is designed around a Markov process with a state vector reflecting the underlying prevalence of prostate cancer in the population, we are able to model exactly such phenomena. This ability to model the decrease in new cancers detected with screening is also essential to modeling the value of repeat versus one-time screening. It is also essential to using the data from the SEER program and other studies to calibrate the model because the relatively recent spread of PSA screening implies that men of different ages today may have had very different past histories of screening.

(4) The effect of benign prostatic hypertrophy and other prostate symptoms and their management on the detection of prostate cancer.

In order to correctly assess the benefits of screening for prostate cancer, one needs to also account for the fact that some cancers will be detected spontaneously even in the absence of screening. One reason for this is that some men will present with symptoms of prostate cancer, but the more important reason is that men may present with symptoms of benign prostatic hypertrophy that will lead either to screening tests or to transurethral resection of the prostate (TURP), which itself can lead to the detection of prostate cancer. The importance of this latter fact should not be underestimated, since about half of patients found during the 1980s were found by this approach.[23] This is likely to have decreased in recent years because of the decreasing use of TURP as a treatment for benign prostatic hypertrophy and increase in the use of PSA screening. Nevertheless, modeling detection by this mechanism remains important, and is essential for using data from periods where TURP was more common to validate the model.

Because our model includes presentation with symptoms and the possibility of detection through TURP, we are able to model these changes and understand their implications for both the costs and effectiveness of prostate cancer screening and treatment.

(5) The potential effects of screening and treatment on quality of life, as measured by quality-adjusted life expectancy.

Another important aspect of our model is that it includes the effect of prostate cancer and prostate cancer treatment on quality of life and costs. Because our model was developed in order to assess the cost-effectiveness of prostate cancer screening and treatment, we included in the model the effects of treatment and progressive disease on several key aspects of quality of life including impotence, incontinence, and pain due to metastatic disease, and the effects of these factors on quality-adjusted life expectancy. Indeed, these quality of life factors are likely to prove crucial determinants of the overall cost-effectiveness of screening and treatment for prostate cancer. Because our model includes quality of life factors as well as costs, we are well situated to use the model for cost-effectiveness analyses.

We extensively documented one of our parameter justifications in the paper "Patterns of prostate cancer treatment by clinical stage and age in the United States," which has been accepted for publication by the American Journal of Public Health.

Task 4: Sensitivity Analysis: Months 6-18

- *a) All parameters in model*
- *b) One and multi-way sensitivity analysis*
- *c) Assess effects on:*
  - *1) Costs*
  - *2) Effectiveness*
  - *3) Cost-effectiveness*

We have presently programmed the model to account for the above stated sensitivity analyses. Since the computing time needed for these analyses is greater than expected – optimizing the model to obtain maximum likelihood estimates can take well over a month of continuous high speed computer time – we have received a no-cost extension to give us more time to allow the computers to optimize our model.

As we stated in our last annual report, we have spent a great deal of time investigating the theoretical basis of cost-effectiveness analysis.[24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40] We completed a number of manuscripts on cost-effectiveness analysis, as listed in the **Reportable Outcomes** section below. These papers examine the purposes for which sensitivity analysis is performed in medical cost-effectiveness analysis and the implications of expected utility maximization models for the methods to perform such analyses. In addition, as stated in previous reports, we have done a great deal of research on determining patient utilities for different states with prostate cancer and treatment complications for the cost-effectiveness analysis. In general, utility assessment is a formal measurement of patients' preferences for their health states. It reflects the strength of the preference or the degree of abhorrence for the potential outcome of interest. Utilities are usually expressed numerically from 1.0 (utility for perfect health) to 0.0 (utility for death). The most common method of utility assessment is the time trade-off method. In time trade-off, patients are asked to estimate the survival time they are willing to sacrifice in order to retain perfect health. In our model, as in other Markov analyses, utility values are associated with each state of health. Studies that address utility in prostate cancer patients were identified by Medline search. We have currently reviewed numerous studies that use time-trade off questions to assess patient utilities.[8,12,14,41,42,43,44]

In addition, we have programmed our model to run analyses that incorporate future costs into the cost-effectiveness analyses. As stated in previous reports, we have shown the importance of including future medical and non-medical costs in cost-effectiveness analysis.[29,32,45] Briefly, these techniques involve adding costs associated with non-prostate cancer related medical expenditures and non-medical consumption net of earnings to total costs accumulated in each years of life. The data to complete these calculations are available from the Consumer Expenditure Survey and Current Population Survey. These will be adjusted to current dollars using the Overall Consumer Price Index (CPI), which we use instead of the medical CPI because of known bias in the medical CPI related to technical change.[46] After the models are fully optimized, we expect that including future costs in our analyses will confirm our hypothesis that screening and treatment interventions that have relatively small effects on quality-adjusted life expectancy compared to life expectancy will be most adversely affected by inclusion of future costs and therefore that inclusion of future costs will reveal interventions that minimize side effects of treatment to be most favorable for prostate cancer.

Finally, we will implement sensitivity analyses that account for the uncertainty in the values of the parameter estimates we derived from literature review, meta-analyses, and secondary data analysis. To do this, we have programmed the model to adjust parameter estimates by three levels, our best estimates of the actual probabilities and estimates that we believe to be the upper and lower boundaries of the parameters. For some of the estimates we use 95% binomial confidence intervals, such as the probability that a man has a TURP given that he has BPH. For other parameters, we use the upper and lower bounds of estimates cited in the literature. Quality of life weights, such as the quality of life associated with the prostate cancer treatment complications of incontinence and impotence, do not lend themselves to analytical bounds, as is the case with binomial probabilities. Hence, the use of the range of estimates in the literature for sensitivity analysis is more appropriate.

Task 5: Estimation of Transition Rates Using SEER and Watchful Waiting Data, Months 12-24

a) Programming of estimation techniques

b) Data cleaning

c) Estimation

d) Sensitivity Analyses

We are currently finishing this task as planned. Again, as stated under our progress report for *Task 4*, since the computing time needed for these analyses is greater than expected – optimizing the model to obtain maximum likelihood estimates can take well over a month of continuous high speed computer time – we have received a no-cost extension to give us more time to allow the computers to optimize our model.

The most important part of this task is estimating the transition probabilities between stage, grade, and death as necessitated by our model. Indeed, for most of the parameters, estimation by literature review is sufficient to determine the probabilities. However, no study has information on the transition probabilities of stage and grade in men who have undetected prostate cancer. As such we use two methods to determine the underlying prostate cancer transition probabilities. In one method, we use constrained optimization to reduce the sum of squares difference between our predicted aggregate incidence and mortality data and SEER aggregate incidence and mortality data. Figure 1 shows an example of what this looks like during the process of fitting. As we can see in the figure, the predicted mortality results and clinical stage results do not completely match the SEER results. However, as we optimize our model, the difference between the predicted and actual incidence and mortality decline. Another way that we are maximizing the model is through the use of maximum likelihood methods and individual level SEER data. With individual level maximum likelihood, we determine the analytic probability that a person in SEER will have an observed detection pattern, treatment pattern, and mortality pattern according to the probabilities of our decision model; the product of these probabilities thus become the maximum likelihood function. Once we have constructed the maximum likelihood function, we use the programming language GAUSS to optimize our model given these probabilities. As our computer program slowly but carefully fits our aggregate level optimization, we are simultaneously working on developing the individual level maximum likelihood optimization. The benefit of the individual level maximization over constrained optimization is that individual level optimization more precisely fits our data and is more likely to result in transition probabilities that are unique. Constrained optimization leads to curve fitting that looks good, but might not fit all of the data, particularly in subgroups, such as young men, where there is not a lot of data. Hence, constrained optimization might lead to different transition probability results depending on the starting point of the model. Once the constrained optimization and maximum likelihood estimations have reached suitable solutions, we will conduct our cost-effectiveness analyses given our best estimates of model parameters and our best high and low estimates.

Task 6: Preparation of Papers Reporting Cost-Effectiveness Analyses, Months 18-30

a) Evaluation of established existing technologies

1)Treatment, esp. of special patient subgroups

2) Rectal

3) PSA

4) Differing screening ages and intervals

b) Evaluations of innovative technologies and management strategies

1) Percent Free-PSA

2) Detection of micrometastases

3) Other technologies

We are currently in the midst of conducting this task and already have some preliminary cost-effectiveness results. We believe that our models are sufficiently optimized such that the direction and magnitude of future results with fully optimized models will not deviate substantially from our current estimates, even if the future estimates are more precise. Preliminary analyses of annual screening with DRE, PSA, or their combination suggests they may indeed be cost-effective in terms of cost per life-year saved (Table 1, Panel 1), but other analyses in terms of cost per Quality Adjusted Life-Year (QALY) suggest screening at all ages is dominated by no screening, while others that assign higher quality of life to health states with complications suggest screening may be cost-effective (Table 1, Panel 2). Even more striking are the results in Panel 3, in which the cost per life year saved of screening at specific ages is examined, and found to be highly cost-effective at only $72,000 per life-year saved at ages 65-69, but strikingly less cost-effective at older ages, reaching for example, about $300,000 per life-year saved by ages 75-59. Such results are of course, only illustrative of the types of results we may find when our final analysis is complete. In performing our final analyses, we will perform extensive sensitivity analyses as described above. Because we expect our results in terms of the cost per QALY to be particularly sensitive to assumptions about the quality of life associated with specific health states, in addition to performing sensitivity analyses we will also

report results that describe the actual likelihood of specific complications with different treatment options. This will permit patients and physicians who differ with respect to their assessments of the importance of specific complications to make independent judgements based on our findings.

In addition to our work undergone to complete this project, we submitted an R-01 in October to expand on this work by examining the cost-effectiveness of different treatment policies under currently mortality trends, and expected mortality trends. We believe that this pending R-01 grant will allow us to continue this important work and explore unanswered questions concerning how the cost-effectiveness of prostate cancer screening and treatment changes as mortality rates decline in the future.

We are excited that we are at the stage of our work in which we have obtained preliminary findings. We are confident that we will be able to have papers stemming from our project under review at peer reviewed journals within the next few months.

FIGURE 1: Model Simulation Results Compared with SEER Data

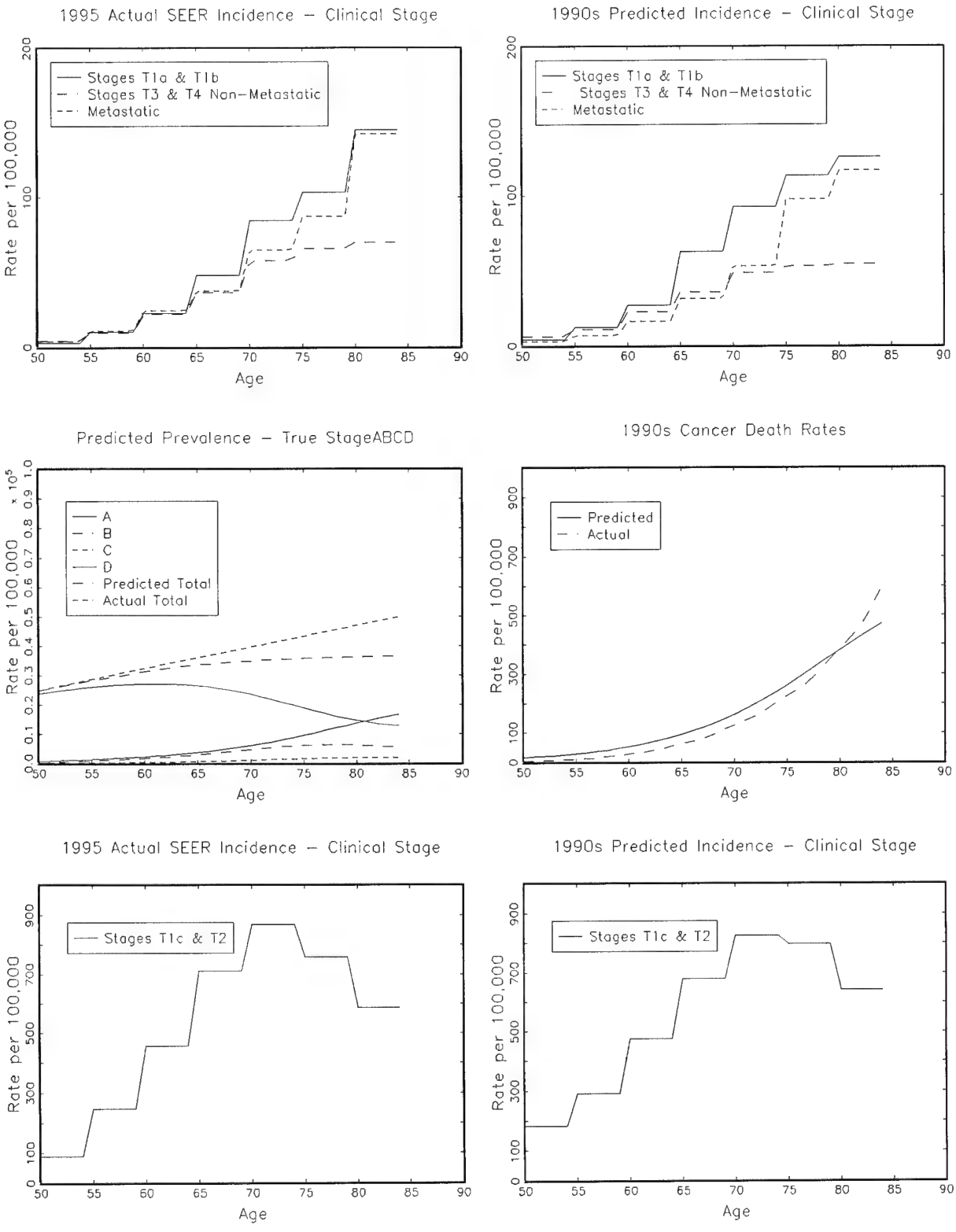

Table 1. Cost-Effectiveness Analyses

Panel 1 - Cost-Effectiveness of Yearly Screening of All Men Over 50

Screening	Cost	Marginal Cost	Life-Years	Marginal Life-Yrs	Incremental Cost-Effectiveness Ratio 1000$ / Life Year	C-E Ratio vs. No Screening 1000$ / Life Year
None	608	-	17.6375	-	-	-
DRE	2009	1401	17.6556	0.0181	77.4	77.4
PSA	2219	210	17.6622	0.0066	31.8	65.2
Both	2766	547	17.6688	0.0066	82.9	68.9

Panel 2 - Cost-Effectiveness of Yearly Screening of All Men Over 50

Complication Quality of Life Assumed to be 0.075 Less than Age-Specific Healthy Quality of Life Weights

	Cost	Marginal Cost	QALYs	Marginal QALYs	Incremental Cost-Effectiveness Ratio 1000$ / QALY	C-E Ratio vs. No Screening 1000$ / QALY
None	608	-	15.6844	-	-	-
DRE	2009	1401	15.6970	0.0126	111.2	111.2
PSA	2219	210	15.7006	0.0036	58.3	99.4
Both	2766	547	15.7054	0.0048	114	102.8

Panel 3 - Cost-Effectiveness of Yearly Screening with Both PSA and DRE within Specific Age Groups

	Cost	Marginal Cost vs. No Screening	Life-Years	Marginal Life-Yrs vs. No Screening	C-E Ratio vs. No Screening 1000$ / Life Year
None	608	0	17.6375	0.0000	0
Age 65-69	1375	768	17.6481	0.0106	72.4
Age 70-74	1313	705	17.6435	0.0060	117.5
Age 75-79	1088	481	17.6392	0.0017	282.9
Age 80-84	837	229	17.6378	0.0003	764.8
Age 85+	792	185	17.6376	0.0001	1846.7

DRE=Digital Rectal Exam, QALY=Quality-Adjusted Life-Year

All costs, life-years, and QALYs are discounted by 3%

(6) Key Research Accomplishments:

- Conducted an extensive literature review and analytic methods in order to estimate most parameters in our model.
- For those parameters that we have not been able to estimate directly, we are currently estimating through constrained optimization and maximum likelihood of our model.
- Completed preliminary cost-effectiveness analyses that indicate that screening is cost-effective in terms of life years.
- Completed preliminary cost-effectiveness analyses that indicate that screening is cost-effective in terms of QALYs only if the quality of life resulting from screening and treatment decisions is high.
- Had a paper on prostate treatment patterns accepted by the American Journal of Public Health. In a previous report, we listed the paper as under review.

(7) Reportable Outcomes:

*Pending R-01. Cost-Effectiveness of Prostate Cancer Screening and Treatment. NIH Submission 10/1/00

Articles:

*Meltzer D, Egleston BL, Abdalla I. Patterns of Prostate Cancer Treatment by Clinical Stage and Age in the United States. *American Journal of Public Health*; in press.

*Meltzer D. Implications of expected utility maximization for assessing cost-effectiveness under uncertainty: Methods for sensitivity analysis and implications for the use of cost-effectiveness analysis to set priorities for medical research. *Journal of Health Economics*; In press.

*Meltzer D, Johannesson M. Inconsistencies in the 'Societal Perspective' on Costs of the Panel on Cost-Effectiveness in Health and Medicine. *Medical Decision Making* 1999; 19:371-377.

*Meltzer D, Johannesson M. On the Role of Theory in Cost-Effectiveness Analysis: A Response To Garber, Russell, and Weinstein. In press, *Medical Decision Making* 1999; 19:383-384.

Published Abstracts

*Meltzer D, Hazen G, Johanesson M, Abdalla I, Chang R, Elstein A, Schwartz A. Effect of Future Costs on the Cost-Effectiveness of Life Extension and Quality of Life Improvement Among the Elderly. *Medical Decision Making* 18: 475, October 1998.

*Meltzer D, Polonsky T. Do Quality-Adjusted Life Years Reflect Patient Preferences? Validation Using Revealed Preference for Intensive Treatment of Insulin-Dependent Diabetes Mellitus. *Medical Decision Making* 18: 459, October 1998.

Presentations:

"Implications of Expected Utility Maximization for Assessing Cost-Effectiveness under Uncertainty: Methods for Sensitivity Analysis and Implications for the Use of Cost-Effectiveness Analysis to Set Priorities for Medical Research". National Bureau of Economic Research Summer Institute, Boston, MA, July 1998.

"Effect of Future Costs on the Cost-Effectiveness of Life Extension and Quality of Life Improvement Among the Elderly", Society for Medical Decision Making Annual Meeting, Plenary Address, Boston, MA,

October 1998.

"Accounting for Future Costs from a Societal Perspective in Cost-Effectiveness Analysis": Plenary Address, International Health Economics Association Annual Meeting, Rotterdam, Netherlands, June 1999.

"Measuring the Burden of Illness". Invited Presentation to Dr. Harold Varmus and panel of experts convened at NIH in Response to IOM Report on Scientific Priorities at NIH, June 1999.

(8) Conclusions:

We have completed the estimation of all parameters in the model that are not being estimated by maximum likelihood estimation. We have written a preliminary draft of our parameter justification document that details the methods we used to determine these parameters; these methods include literature review, meta-analysis, secondary data analysis, and mathematical simulations. We are currently using constrained optimization and maximum likelihood techniques to determine the stage, grade, and mortality transitions associated with prostate cancer. Because the computing time for these optimizations is greater than expected, we have received a no-cost extension of our deadline from the Department of Defense. Once these models have fully optimized, we will be able to run cost-effectiveness analyses and associated sensitivity analyses in order to determine precise estimates of the cost-effectiveness of screening policies. Initial analyses indicate that screening is cost-effective in terms of life-years saved, but that it is not necessarily cost-effective in terms of QALYs. We have submitted an R-01 through which we hope to expand our work to include an analysis of the cost-effectiveness of prostate cancer treatments under expectations of future increases in life expectancy.

So what do our findings mean for the future of the field?

- We have developed the most extensive decision analytic model to date of the natural history, screening, and treatment of prostate cancer and validated the model using SEER data. In particular our model is an improvement on other models in that it accounts for:
  (1) Tumor heterogeneity and progression rates by grade,
  (2) Misclassification of tumor stage due to the discrepancy between clinical and pathologic stage.
  (3) The ability of screening and treatment to affect the prevalence of prostate cancer.
  (4) The effect of benign prostatic hypertrophy and other prostate symptoms and their management on the detection of prostate cancer.
  (5) The potential effects of screening and treatment on quality of life, as measured by quality adjusted life expectancy.
- We have begun to conduct preliminary cost-effectiveness analyses which indicate that prostate cancer screening is cost-effective in terms of life-years saved, but not necessarily cost-effective in terms of QALYs due to complications that result from treatment. This suggests that innovations that reduce the side effects of prostate cancer treatment will make treatment much more cost-effective.

(9) References

[1] Glynn RJ, Campion EW, Bouchard GR, Silbert JE. The development of benign prostatic hyperplasia among volunteers in the normative aging study. American Journal of Epidemiology 1985, 121(1):78-90

[2] Love RR, Fryback DG. A Cost-Effectiveness Analysis of Screening for Carcinoma of the Prostate by Digital Examination. Medical Decision Making 1985; 5(3):263-278.

[3] Carlsson P, Pedersen KV, Varenhorst E. Costs and benefits of early detection of prostatic cancer. Health Policy 1990; 16:241-253.

[4] Mold JW, Holtgrave DR, Bisonni RS, Marley DS, Wright RA, Spann SJ. The Evaluation and Treatment of Men with Asymptomatic Prostate Nodules in Primary Care: A Decision Analysis. The Journal of Family Practice 1992; 34(5):561-568.

[5]Fleming C, Wasson JH, Albertsen PC, Barry MJ, Wennberg JE. A Decision Analysis of Alternative Treatment Strategies for Clinically Localized Prostate Cancer. JAMA 1993; 269(20):2650-2658.

[6] Littrup PJ, Goodman AC, Mettlin CJ. The Benefit and Cost of Prostate Cancer Early Detection. CA-Cancer Journal for Clinicians 1993; 43:134-149.

[7] Littrup PJ, Kane RA, Mettlin CJ, Murphy GP, Lee F, Toi A, Badalament R, Babaian R. Cost-Effective Prostate Cancer Detection: Reduction of Low-Yield Biopsies. Cancer 1994; 74(12):3146-3158.

[8] Krahn MD, Mahoney JE, Eckman MH, Trachtenberg J, Pauker SG, Detsky AS. Screening for prostate cancer: A decision analytic view. JAMA 1994; 272(10): 773-80.

[9] Cowen ME, Chartrand M, Weitzel WF. A Markov Model of the Natural History of Prostate Cancer. Journal of Clinical Epidemiology 1994; 47(1):3-21.

[10] Optenberg SA, Thompson IM. Economics of Screening for Carcinoma of the Prostate. Urologic Clinics of North America 1990; 17(4): 719-737.

[11] Benoit RM, Naslund MJ. An Economic Rationale for Prostate Cancer Screening. Urology 1994; 44(6):795-803.

[12] Cantor SB, Spann SJ, Volk RJ, Cardenas MP, Warren MM. Prostate Cancer Screening: A Decision Analysis. The Journal of Family Practice 1995; 41(1):33-41.

[13] Barry MJ, Fleming C, Coley CM, Wasson JH, Fahs MC, Oesterling JE. Should Medicare provide reimbursement for prostate-specific antigen testing for early detection of prostate cancer? - Part IV: Estimating the risks and benefits of an early detection program. Urology 1995; 46(4):445-461.

[14] Kattan MW, Cowen ME, Miles BJ. A decision analysis for treatment of clinically localized prostate cancer. Journal of General Internal Medicine 1997; 12:299-305.

[15] Ross KS, Carter HB, Pearson JD, Guess HA. Comparative efficiency of prostate-specific antigen screening strategies for prostate cancer detection. JAMA Sept. 20, 2000, 284(11):1399-1405.

[16] Etzioni R, Cha R, Cowen ME. Serial prostate specific antigen screening for prostate cancer: A computer model evaluates competing strategies. Journal of Urology 1999; 162:741-748

[17] Chodak GW, Thisted RA, Gerber GS, Jahansson JE, Adlfsson J, Jones GW, Chisholm GD, Moskovitz B, Livne PM, Warner J. Results of conservative management of clinically localized prostate cancer. New England Journal of Medicine 1994; 330:242-248.

[18] Brawer MK. Screening and early detection of prostate cancer will decrease morbidity and mortality from prostate cancer: the argument for. [Review] European Urology. 29 Suppl 2:19-23, 1996

[19] Bales GT. Gerber GS. Screening for the early detection of carcinoma of the prostate. PPO Updates. 9(6):1-9, 1995.

[20] Meltzer, DO, B Egleston, I Abdalla. Patterns of prostate cancer treatment by clinical stage and age in the United States. Forthcoming, American Journal of Public Health.

[21] Lu-Yao G, Potosky AL, Albertsen PC, Wasson JH, Barry MJ, Wennberg JE. Follow-up prostate cancer treatments after radical prostatectomy: A population based study. Journal of the National Cancer Institute 1996; 88:166-173.

[22] Partin AW, Kattan MW, Subong EN, Walsh PC, Wojno KJ, Oesterling JE, Scardino PT, Pearson JD: Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA 1997 May 14;277(18):1445-51.

[23] Mettlin C, Jones GW, Murphy GP. Trends in prostate cancer care in the United States, 1974-1990: Observations from the patient care evaluation studies of the American College of Surgeons Commission on Cancer. CA: Cancer J Clin 1993; 43:83-91.

[24]Barry MJ, Fowler FJ Jr, Mulley AG Jr, Henderson JV Jr, Wennberg JE. Patient reactions to a program designed to facilitate patient participation in treatment decisions for benign prostatic hyperplasia. Medical Care 1995; 33:771-782.

[25] Cutler D, Richardson E. Measuring the Health of the U.S. Population. Brookings Papers: Microeconomics 1997:217-271.

[26] Erickson P, Wilson R, Shannon I. Years of Healthy Life. Healthy People 2000 Statistical Notes. Centers for Disease Control and Prevention/National Center for Health Statistics 7, April 1995.

[27] Gold MR, Siegel JR, Russel LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. (New York, NY: Oxford University Press, 1996).

[28] Institute of Medicine. Scientific Opportunities and Public Needs: Improving Priority Setting and Public Input at the National Institutes of Health. (Washington, DC: National Academy Press, 1998).

[29] Johannesson M, Meltzer D, O'Conor R. Incorporating Future Costs in Medical Cost-Effectiveness Analysis: Implications for the Cost-Effectiveness of the Treatment of Hypertension. Medical Decision Making 1997; 17:382-389.

[30] Johannesson M, Meltzer D. Some reflections on cost-effectiveness analysis. Health Economics 1998; 7:1-7.

[31] Manton KG, Corder L, Stallard E. Chronic trends in elderly United States populations: 1982-1994. Proceedings of the National Academy of Sciences 1997; 94:2593-2598.

[32] Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. Journal of Health Economics 1997; 16:33-64.

[33] Meltzer D, Johannesson M. On the Role of Theory in Cost-Effectiveness Analysis: A Response to Garber, Russell and Weinstein. Medical Decision Making. In Press.

[34] Meltzer D. Implications of Expected Utility Maximization for Assessing Cost-Effectiveness under Uncertainty: Methods for Sensitivity Analysis and Implications for the Use of Cost-Effectiveness Analysis to Set Priorities for Medical Research. Journal of Health Economics; under review.

[35] Meltzer D, Johannesson M. Inconsistencies in the 'Societal Perspective' on Costs of the Panel on Cost-Effectiveness in Health and Medicine. Medical Decision Making; in press.

[36] Meltzer D, Polonsky T, Tobian J. Does Quality-Adjusted Life Expectancy Predict Patient Preferences for Treatment in IDDM: Validating Quality of Life Measures through Revealed Preference. In preparation.

[37] Murphy KM, Topel RH. The Economic Value of Medical Research. Unpublished manuscript, University of Chicago, 1998.

[38] Nord E. Methods for Quality Adjustment of Life Years. Social Science and Medicine 1992; 34:559-569.

[39] Tengs, T. Planning for Priorities Project, No. 2, Progressive Policy Institute, July, 1998.

[40] Weinstein M, Stason WB. Hypertension: A Policy Perspective. (Cambridge: Harvard University Press; 1976).

[41] Fleming C, Wasson JH, Albertsen PC, Barry MJ, Wennberg JE. A decision analysis of alternative treatment strategies for clinically localized prostate cancer. JAMA 1993; 269:2650-2658.

[42] Bennett CL, Chapman G, Elstein AS, Knight SJ, Nadler RB, Sharifi R, Kuzel T. A comparison of perspectives on prostate cancer: analysis of utility assessments of patients and physicians. European Urology 1997; 32(suppl 3):86-88.

[43] Albertsen PC. Hanley JA. Gleason DF. Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 1998; 280:975-980.

[44] Cowen ME, Miles BJ, Cahill DF, Giesler RB, Beck JR, Kattan MW. The danger of applying group-level utilities in decision analyses of the treatment of localized prostate cancer in individual patients. Medical Decision Making 1998; 18:376-380.

[45] Meltzer DO, Egleston B, Stoffel D, Dasbach E. The effect of future costs on the cost-effectiveness of medical interventions among young adults: The example of intensive therapy for type-1 diabetes. Medical Care 2000; 38:679-685.

[46] Newhouse JP, 1992. Medical care costs: how much welfare loss? Journal of Economic Perspectives 6, 3-21.